REMARKS

Claims

Claims 1, 4, 8, 11 and 15–17 are currently under examination with claims 18–20 withdrawn from consideration due to restriction/election and claims 2, 3, 5–7, 9, 10, and 12–15 cancelled without prejudice or disclaimer. Claims 21–24 are added by this paper.

Claim amendments

Amended claim 1 now incorporates the subject matter of claims 3 and 7, which are hereby cancelled. Amended claim 8 now incorporates the subject matter of claims 10 and 14, which are hereby cancelled.

The claims have been amended to recite language in accordance with conventional US practice. The amendment of claim 16 is supported, at least, by the disclosure contained in page 17, ¶2 and ¶3 of the originally-filed specification.

Use claims 19 and 20 have been amended to recite US process claims.

New claim 21 is supported by the disclosure contained in, for example, the paragraph bridging pages 22 and 23 of the originally-filed specification. New claims 22–24 are supported, at least, by the disclosure contained in the Examples.

It is respectfully submitted that the claim amendments do not raise new matter. Entry thereof is earnestly solicited.

Rejection under §112, ¶2

The forgoing amendments render the rejection of claims 1, 8, 12–17 under this section moot. Withdrawal of the rejection is respectfully requested.

Applicants disagree with the contention that antibody variants are not known. The specification provides adequate written description of such molecules, including techniques for obtaining and testing the property (for example, binding activity) of such molecules. See the paragraph bridging pages 10 and 11 of the originally-filed specification and the references cited therein. However, purely in order to facilitate the prosecution of the instant application, Applicants have amended the claim language to recite specific antibody molecules. Applicants' amendment of the claims is not to be construed as acquiescence to this or any other ground of rejection. Withdrawal of the rejection is respectfully requested.

IDS

Copies of missing non-patent literature references are enclosed.

Specification

The Examiner is thanked for her careful review of the specification. The minor typographical error has been corrected. Withdrawal of the objection is respectfully requested.

The specification has been amended to claim priority to the earlier-filed US provisional application. Entry thereof is earnestly solicited.

Rejections under §102

Claims 8–10 and 13–17 are rejected under §102(b) as allegedly anticipated by Mahler (WO 03/007988). Claims 1–4, 8–11 and 15–17 are rejected under §102(a) as allegedly anticipated by Kaisheva et al. (US pat. pub. No. 2003/0138417; published: July 24, 2003). These contentions are respectfully traversed.

Mahler (WO 03/007988; which corresponds to US patent application publication No. 2004/0170632) teaches formulations of cetuximab, a chimeric monoclonal antibody against the endothelial growth factor receptor (EGFR). See, ABSTRACT of the cited reference. It is taught in the last paragraph at page 4, lines 15–17 of WO 03/007988 that the concentration of the chimeric monoclonal antibody in such formulations is present in a concentration of from 0.1 mg/ml to 25 mg/ml. Preferably, the antibody concentration is from 2 mg/ml to 10 mg/ml and particularly preferably about 5 mg/ml. See, paragraph [0015] of the US publication. The reference is silent with regard to a highly concentration, liquid formulation comprising monoclonal antibody c225 (Mab c225), wherein the concentration of said antibody in said formulation is 50 mg/ml to 180 mg/ml. Since Mahler fails to teach or disclose all the elements of Applicants' claims, the cited reference cannot anticipate the subject matter of the present claims. Withdrawal of the rejection is respectfully requested.

Kaisheva is directed to liquid pharmaceutical formulation comprising a high concentration, e.g. 50 mg/ml or more, of immunoglobulin G (IgG) antibody in buffer solutions. See, ABSTRACT of Kaisheva et al. In the "Summary of the Invention" section, the reference discloses that antibodies that can be formulated in high concentrations are daclizumab (a humanized anti-IL-2 receptor monoclonal antibody), HAIL-12 (a humanized anti-IL-12 monoclonal antibody), HuEP5C7 (humanized anti-L selectin monoclonal antibody) or Flintozumab (humanized anti-gamma interferon monoclonal antibody). There is no mention of highly concentrated, liquid formulations comprising anti-EGFR antibodies, or more specifically, formulations comprising monoclonal antibody c225 (Mab c225) or monoclonal antibody h425 (Mab h425). See, amended claims 1 and 8. Absent such

teaching, the cited reference cannot anticipate what is claimed herein. Withdrawal of the rejection is respectfully requested.

Rejection under §103

Claims 1–17 are rejected under §103(a) as allegedly rendered obvious by Sridhar (*Lancet Oncology*, 2003) in view of Arvinte et al. (WO 02/96457). Reconsideration is respectfully requested.

Sridhar et al. disclose EGFR antibodies (including EMD72000) in clinical trials as cancer therapies. As conceded by the Examiner in the last complete paragraph at page 6 of the Office Action, "Sridhar et al. do not discuss antibody formula concentrations or the means of concentrating an antibody formulation." The Office Action at page 6 alleges that this aspect is rectified by Arvinte's teachings of concentrated antibody preparations. This contention and the rejection based thereon are both respectfully traversed.

The cited secondary reference of Arvinte (WO 02/096457) discloses anti-IgE antibodies. Arvinte generically discloses antibodies that bind to a very broad target, for example, immunoglobulin molecules. There is no teaching or suggestion of antibodies having specific epitopes (such as EGFR). The reference is especially silent on monoclonal antibodies, such as, Mab c225 and Mab h425, as claimed herein. Moreover, neither Sridhar nor Arvinte provides any hint or suggestion that the antibodies of the present invention (i.e., Mab C225 or Mab h425) can be prepared as highly concentrated formulations. As such, Sridhar in view of Arvinte fails to render obvious the claims of the instant application.

An aspect of the present invention is directed to the preparation of highly concentrated, liquid formulations of Mab c225 and Mab h425 as stable, ready-to-use solutions having low viscosity, low application volumes (for use as pharmaceutical preparations) and that are applicable for subcutaneous administration. Preparation of highly concentrated, liquid formulations of antibodies are afflicted with technical challenges and routine protocols for protein concentration are not always applicable for large proteins with specific properties, such as, monoclonal antibodies. The methods of the present invention allow for the preparation of highly concentrated, liquid formulations of the aforementioned anti-EGFR antibodies, and the ready formulation thereof as pharmaceutical preparations and/or kits for therapeutic and diagnostic applications. Arvinte generically discloses methods for obtaining high concentrations of proteins, but the proteins are non-specific antibody molecules that do not have specific epitopes. The primary reference discloses the claimed antibody molecules in very low concentrations. As such, the antibody preparations, compositions, kits of the present invention, including methods for obtaining such are inventive over the cited references. Withdrawal of the rejection is respectfully requested.

The following comments are additionally provided to rebut the Examiner's reliance on other art references, as made of record in the IDS filed July 11, 2007.

Applicants submit that aforementioned Mahler (WO 03/007988) fails to rectify the limitations in Sridhar and/or Arvinte with respect to *prima facie* case of obviousness, had there been one. For example, in view of the amendment of the claims, it is earnestly submitted that neither Mahler nor Sridhar provides any hint or suggestion that antibody preparations comprising Mab c225 or Mab h425 can be prepared as highly concentrated, liquid formulations. As such a combination of the aforementioned references, even at their broadest interpretation, fails to render obvious the claims of the present application.

US patent no. 6,252,055, which the Office Action cites at page 7 as allegedly being cumulative with the above-cited Arvinte et al. (WO 02/96457), discloses formulations off campath-1 H. In column 2, the '055 patent explicitly teaches that highly concentrated formulations of polyclonal antibodies can be prepared (with a high content of stabilizers); however, monoclonal antibodies poses a difficult problem with respect to high concentration, especially if pharmaceutically critical stabilizers should be omitted. As such, a combination of the above-cited Sridhar or Mahler and US 6,252,055 does not lead a skilled worker to highly concentrated formulations of monoclonal antibodies such as, for example, Mab c225 or Mab h425 of the present invention. Rather, the disclosure therein leads a skilled worker away from the present invention. Therefore the Examiner's reliance on the '055 patent is legally misplaced.

Obviousness-type double patenting rejection

Claims 1–3, 5–10 and 12–17 are rejected under the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 1–13, 15-24 and 26–27 of US application no. 10/996,597 in view US patent no. 6,171,586. Positive actions are not necessary since the rejection is provisional in nature. If required, Applicants will address this rejection once allowable subject matter is identified.

Applicants bring the Examiner's attention to WO 2004/085474 (Tarnowski et al). A copy of the publication is enclosed herewith for the Examiner's review.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

/Sagun KC/

Sagun KC, Reg. No. L0510
Agent for Applicant(s)

/Anthony J. Zelano/

Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

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